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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,897	07/20/2000	Richard W. Scott	CEPH-1066	4645

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/621,897	SCOTT ET AL.	
	Examin r	Art Unit	
	Dave Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-42,44,46-64 and 77-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-42,44,46-64 and 77-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Claims 1-38 and 65-76 have been canceled, claims 43 and 45 have been canceled, claims 39-42, 44, 46-52 and 57-60 have been amended, claims 77-98 have been added by the amendment filed June 25, 2002.

Claims 39-42, 44, 46-64 and 77-98, to which the following ground of rejection is applicable, are pending.

In view a further consideration of the state of the prior art, the as-filed specification, the nature of the invention, the breadth of the claims, the working examples, and the level of a skilled artisan at the time the invention was made, the previous office action of record has been vacated by the examiner. Following is a new ground of rejection under 35 USC 112, first paragraph, wherein only the exemplified mouse model is reasonably enabled by the as-filed specification at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-42, 44, 46-64 and 77-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said rodent comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide

having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type mouse.

does not reasonably provide enablement for any other claimed embodiment embracing any other non-human transgenic non-human mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to a gene-targeted rodent (a knock-in rodent, wherein a particular endogenous gene is targeted for replacement by homologous recombination, *e.g.,* homologously targeted for accepting a DNA sequence encoding a functionally active PS-1 protein comprising any mutation as listed in claim 97, and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, which targeted rodent is still a transgenic mouse) heterozygous or homozygous for FAD PS-1 mutation comprising a human p264L mutation and for the Swedish APP695 mutation, or a method for screening chemical compounds for the ability to decrease *in vivo* level of A-beta42 peptide, obtaining a tissue sample from said mouse, *e.g.,* brain tissue, non-brain tissue, and body fluids, and measuring the relative amount of A-beta42 peptide in the tissue sample. The specification (pages 37-39) coupled with knowledge in the prior art only provides sufficient guidance and/or evidence for one skilled in the art to make and use the claimed invention directed to A gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said mouse comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type mouse.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of

the claims.

The newly amended claims are readable on any gene-targeted non-human rodent heterozygous or homozygous for human Familial Alzheimer's disease (AD). The specification contemplated that the claimed gene-targeted rodent for any presenilin-1 (PS-1) mutation and Swedish mutation either exhibits the pathology and symptomatology of ADA, or can be used in a screening assay to screen for *in vivo* inhibitors and for discovering and testing the efficacy and suitability of putative chemicals compounds for their ability to inhibit the formation of Aβ42 peptides in the brain tissues, other tissues, and body fluids. However, the specification does not provide sufficient guidance and/or evidence to demonstrate any of the contemplated properties, *e.g.,* ADA phenotypes and/or P264L- and Swedish APP695 knock in mice that exhibits an increase of endogenous Aβ42 peptides relative to that of wild-type mice, let alone a rodent as broadly claimed, and/or any other mouse that does not comprise the P264L in the PS-1 gene and a human APP polypeptide having the Swedish APP695 mutation. While the state of the art of transgenics is such that one skilled in the art can deliver and express a gene in a desired animal, it is not reasonably predictable for one skilled in the art to produce any transgenic mammal other than the exemplified mouse that exhibit a desired phenotype, regardless whether a gene targeted modification technique rather than a traditional introduction of a desired exogenous protein encoded construct into embryonic cells. Applicants contemplates that by targeting any DNA vector construct encoding any mutant PS-1 gene product (human PS1 mutant cDNA as listed in claim 97, for example) or a human APP polypeptide comprising the Swedish mutation via homologous recombination into an endogenous genomic site containing the endogenous PS1 gene of any murine cell including murine pluripotent, murine embryo-derived stem (ES) cells, an genetically modified ES cell, for example, can be produced and can be employed to produce a knock-in non-human mammal comprising germ-line chimera as the result of fusion between the genetically modified ES cell and the mouse embryos (page 10). The specification further provides working examples showing the making by ES technology and cross-breeding of a gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said mouse comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a

human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type mouse. However, it is not apparent how such guidance and/or working examples can be reasonably extrapolated to any claimed rodent other than the exemplified mouse, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record. At the time the invention was made, the art of transgenics including gene targeted modification using ES cell technology was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells. Palmiter *et al.* (PNAS, 1991) teach that directed expression of any gene to any specific cell type of an animal by using established transgenic methodology is theoretically possible by combining the regulatory regions(s) of a gene that is expressed in a cell-specific manner with any mRNA-encoding structural gene. Palmiter *et al.,* note, however, that not all gene constructs work well; the two most common problems are inappropriate expression patterns and failure to achieve adequate expression levels (page 478, left column, first paragraph). Wall (Theriogenology, 1996) discloses the unpredictability of transgene behavior due to factors such as unidentified control elements (during the fusion between ES cell and murine embryos) and may result in variable expression. Whitelaw *et al.* (Transgenic Research , 1991, page 10, column 1 bridging column 2) indicates that exogenous DNA. constructs, intronless constructs or constructs containing the introns, do affect variation in gene expression. Palmiter (Ann Rev. Genes, 20, p. 465-498) indicates that variable or inappropriate expressions do often occur in transgenic founder animal and/or offspring (pages 482 and 483).

More specifically as to the lack of reasonable correlation between rodent and other species in ES technology, Polejaeva *et al.* (Theriogenology, Vol. 53, pages 117-126, 2000), states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear

> microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke *et al.* disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Heprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic rodent comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic rodent than the exemplified mouse, the state of the art supports that only rodent ES cells were enabled for used in the production of transgenic rodent. Taken together, the current status of transgenic art is such that generating transgenic non-human mouse with a requisite phenotype, *e.g.,* FAD, is neither routine nor predictable, unless proven by a working example, let alone a claim that embraces any transgenic non-human mammal other than rodent as claimed. It is apparent that neither the as-filed application nor any of the prior art of record provides any evidentiary support so as to reasonably extrapolate from the exemplified mouse to the full breadth of the claimed invention as presently claimed. As such, a skilled artisan would not accept the making and use of any claimed rodent is reasonably predictive at the time the invention was made.

Furthermore, the specification provides limited guidance on page 5 with regard to phenotypic expression of the P264L mutation. The specification indicates that the P264L mutation <u>in humans</u> caused an increased amount of amyloid A-beta42 protein, and is involved in clinical manifestation of Alzheimer's

disease (AD). However, neither the specification nor its incorporated references provides any teaching on any biological effect on the amount of murine amyloid A-beta42 protein expression or clinical manifestation of AD in the mouse of the invention. Note that incorporation and expression of a human P264L mutant PS1 encoded construct as a foreign genetic construct into any murine cell which is subsequently used for fusion with a murine embryo so a to produce a founder genetically modified mouse does not necessarily mean a reasonable predictability of a phenotypic expression in the founder transgenic mouse for any detectable phenotype and/or phenotypic offspring thereof. Furthermore, there is no evidence either from the specification or from the prior art that an correct introduction via homologous recombination of a human mutant P264L PS-1 gene into a mouse having a murine genome encoding distinct murine proteins, and having a distinct physiology and chemical pathways would generate any phenotype of FAD.

In other words, while the specification provides sufficient guidance and/or assay systems to screen for *in vivo* inhibitors and for discovering and testing the efficacy and suitability of putative chemical compounds for their ability to inhibit the formation, presence, and deposition of excessive amounts of A-beta42 in any tissues obtained from the claimed transgenic mouse, no specific teachings regarding any other phenotype associated with AD and expressed in any claimed rodent transgenic mammal are disclosed.

The data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility. This conclusion coupled with state of the art is consistent with a finding of lack of enablement for the practice of what is claimed. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, the present claims are properly rejected under 35 U.S.C. 112, first paragraph.

It is noted that applicant's response (page 9-10) states that to advance the prosecution of this application, all claims have been amended to limit to a rodent as presently claimed. However, the previous office action was not correct in assessing the enabled scope of the claimed invention, particularly since there is no evidentiary support as a whole to reasonably extrapolate from applicant's exemplified mouse to

any other mouse as embraced by the claimed invention, *e.g.,* claim 97, let alone any other rodent as presently claimed. As such, this office action has been made non-final so that applicant would have an opportunity to address the issues as now stated in this rejection.

To the extent that applicant's response is relevant to the stated rejection, the response has been considered but is not found persuasive because of the following reasons:

Applicant asserts on page 10 that Applicant's claims do not require that the claimed rodents exhibit symptoms of FAD or any other phenotype. However, claim 39, for example, states:

> A gene-targeted, non-human rodent heterozygous for a human Familial Alzheimer's Disease (FAD) mutation...

As claimed explicitly within the context of the 'human Familial Alzheimer's Disease (FAD) mutation' present in the mouse, the claimed invention does embrace a rodent that not only exhibit an increased levels of Aβ42 peptides but also manifests a pathology and symptomatology of ADA, when read in light of the as-filed specification. Also see claims 58-60 for evidence indicating that Applicant's claims do require that the claimed rodents exhibit symptoms of FAD.

A simple amendment by deleting the phrase "a human Familial Alzheimer's Disease (FAD) mutation" would obviate this particular issue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned

at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 39-42, 44, 46-64, 97, 98 are rejected under 35 USC 103(a) as being unpatentable over Duff *et al.* (US Pat No. 5,898,094) taken with US Pat No. 5,850,003.

Duff *et al.* teach a transgenic mouse (homozygous or heterozygous) comprising in its genome both a human mutation of the presenilin-1 (PS-1 gene), M146L, and the Swedish APP695 mutation heterozygous and/or homozygous, screening methods, and a phenotype of elevated levels of gene-targeted (β-amyloid) peptides (Claims, columns 5, 6, and 9-11, particularly column 7). Duff *et al.* do not teach explicitly that the parental mouse employed in crossing so as to produce a double transgenic mouse is produced by gene-targeted technique, Duff *et al.* do teach on the first paragraph of column 7 that gene targeted technology can be used to make a transgenic mouse as envisioned by Duff *et al.* In addition, US Pat No. 5,850,003 discloses a gene-targeted transgenic mouse comprising a Swedish mutation including the Swedish APP695 mutation, which also results in an elevated level of Aβ peptides, screening methods, *e.g.,* columns 12, 15, 16, 23, 24. Thus, it would have been obvious for one of ordinary skill in the art to have made a gene targeted double transgenic mouse comprising in its genome both the presenilin-1 (PS-1 gene), M146L, and the Swedish APP695 mutation so as to enhance or induce abnormal and elevated levels of β-amyloid in the brain of mice, and to further use the mice for production of antisera or antibodies to both the M146L and/or APP695. One would have been motivated to have made a double and gene targeted transgenic mouse containing both the mutations because Duff teaches that gene targeted technology can be used to make a transgenic mouse, and that the double transgenic mouse accelerated formation of deposits containing Aβ, and because the '003 patent provides evidentiary support showing that it is common in the prior art to use homologously gene targeting construct to make transgenic mice

containing a Swedish mutation including the Swedish APP695 mutation, wherein the mouse can be used in screening assays and for production of antisera.

Thus, the claimed invention as a whole was *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 39-42, 44, 46-64, 77-98 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,284,924 taken with Duff *et al.* (US Pat No. 5,898,094), and claims 1-4 of US Pat No. 5,850,003. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims embrace a gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said mouse comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type rodent. While the claims of the '924 patent does not explicitly claim the Swedish mutation in the transgenic mice, it would have been obvious for one of ordinary skill in the art to have made or added the Swedish mutation to the mice of the of the '924 patent so as to enhance or induce abnormal neuropathology which includes an elevated level of Aβ peptides in the brain of mice, as taught in Duff

(Claims, columns 5, 6, and 9-11, particularly column 7) and the '003 patent *e.g.,* columns 12, 15, 16, 23, 24.

Thus, the claims are obvious variants of one another.

No claim is allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER